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(54) Title: FINELY DIVIDED SOLID CRYSTALLINE POWDERS VIA PRECIPITATION INTO AN ANTI-SOLVENT

(57) Abstract

The present invention is a process for producing a finely divided solid which comprises (1) dissolving the solid to be finely divided in a liquid carrier solvent to form an injection solution and (2) adding the injection solution of step (1) to a volume of anti-solvent sufficient to precipitate or crystallize the solid. The solid can be a pharmaceutical, agricultural chemical, commercial chemical, fine chemical, food item, photographic chemical, dye, explosive, paint, polymer or cosmetic.

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FINELY DIVIDED SOLID CRYSTALLINE POWDERS

VIA PRECIPITATION INTO AN ANTI-SOLVENT

BACKGROUND OF THE INVENTION

1. Field of the Invention

5   This invention relates to processes for making finely divided
solid powders such as pharmaceutical and technical chemicals or
explosive agents which are normally difficult to solubilize in
aqueous media or to subdivide without extensive chemical or physical
treatments such as micronizing or repeated grinding operations, or in
10   the case of explosives, hazardous operations. More particularly,
this invention provides a process for producing finely divided solid
crystalline or amorphous powders involving the sub- or super critical
gases which process is not limited by the solubility of the solid in
the pure supercritical gas, per se.

15   2. Description of the Related Art

Adding a normally liquid anti-solvent to a liquid solution of a
solid to be precipitated or subdivided, or of adding the liquid
solution containing the solid to be precipitated or subdivided into
the liquid anti-solvent is a well-known chemical plant practice which
20   is often referred to as the "salting out" effect. See Kirk-Othmer's
ENCYCLOPEDIA OF·CHEMICAL TECHNOLOGY, Third Edition, 7, John Wiley &
Son, Publishers (1979), page 261 in a chapter on "Crystallization".

Adding a solution of a solid dissolved in a good liquid solvent
therefor to a comparatively large volume of poor liquid solvent is
25   known as controlled microprecipitation and is practiced on an
industrial scale for a variety of solid products.

The use of compressed supercritical gas for its solubility
effect on some solids is also an old concept referred to in U.S.
Patent 4,263,253 (column 1), but has become of more recent interest
30   for the production of fine powders. In their review of supercritical
fluid technology, Paulaitis, M.E. et al, "Supercritical Fluid
Extraction", Rev. Chem. Eng., 1 (2) (1983), pp. 179-250, describe the
redistribution of particle sizes of solids via supercritical fluid
nucleation. Krukonis, V. J., "Supercritical Fluid Nucleation of Dif-
35   ficult to Comminute Solids", Paper No. 140f, presented at the Annual
Meeting of the AIChE, San Francisco, Nov. 1984, expands upon that
work.

In U.S. Patent 4,582,731 there is described a process for making

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a finely divided solid using a supercritical fluid as a solvent for
the solid to be subdivided which solution is then expanded into a low
pressure vacuum atmosphere to quickly separate the depressured
supercritical gas solvent from the solid.   This latter work is

5   further described in a paper by Peterson, R.C. et al, "Rapid Precip-
itation ... Supercritical Fluid Solutions; The Formation of Thin
Films and Powders", J. Am. Chem. Soc., 108, 2100-2103 (1986).   The
direct application of supercritical fluid extraction to the produc-
tion of pharmaceutical powders was described by Larson, K.A. et al,

10   "Evaluation of Supercritical ... Industry", Biotech. Prog. 2 (2)
(June 1986), pp. 73-82, and independently by Loth, E. et al, "Proper-
ties ... Supercritical Gases", Int. J. Pharm., 32, 265-267 (1986).

All of these literature and patent descriptions are similar
insomuch as they all teach that the solid compound to be micronized

15   or subdivided must first be dissolved in an appropriate supercritical
fluid.   The supercritical fluid containing the dissolved solute is
then rapidly expanded (flashed) to separate the supercritical gas
from the solid and to recover the dry, micronized powder.

It is also disclosed in Ber. Bunsenges, Phys. Chem., 88, 900

20   (1984) that complex oily, gummy or otherwise highly viscous natural
products such as crude lecithin can be stripped of their more
volatile components by extraction with a supercritical gas, leaving
behind insoluble matter in the form of a recoverable powder (also see
U.S. Patent 4,367,178).   This phenomenon forms the basis of all

25   supercritical solvent leaching operations, where for example the
unextracted mass may be organic matter as in the leaching of coffee
(U.S. Patent 4,247,570) or spice (U.S. Patent 4,123,559).   If coal is
extracted with a mixture of supercritical xylene and tetralin then
the undissolved portion is a particulate ash consisting of organic

30   char and inorganic minerals (U.S. Patent 4,192,731).

A similar but opposite process has been described in the
literature, see Chemical Engineering, July 1989, p 39.   The process
is called the "GAS" (gas-anti-solvent) process and is performed by
adding a supercritical fluid to a premixed volume of dissolved solute

35   dissolved in an organic liquid solvent.   As the supercritical fluid
dissolves in the solution, the solid precipitates out.   A speech
describing the GAS process was given at the American Institute of
Chemical Engineers Annual Meeting on November 29, 1988, (Gas Recrys-

tallization: A new Process to Recrystallize Compounds Insoluble in
Supercritical Fluids; paper No. 48c).

In addition to the above the following patents may be of
interest as illustrating uses or applications of the above background
5   technology.

U.S. Patent 3,981,957 discloses a process for making a high
density polymer powder comprising melting a thermoplastic polymer to
a melt, mixing the polymer melt with a solvent and discharging the
polymer melt/solvent mixture through a nozzle in contact with a
10   blowing gas such as nitrogen. There is no mention of the use of a
supercritical solvent or a supercritical anti-solvent procedure.

U.S. Patent 4,012,461 discloses a process for producing polymer
powders which includes the step of atomizing a polymer slurry into a
vaporization zone on the presence of a drying gas. There is no
15   mention of the use of a supercritical gas anti-solvent procedure.

U.S. Patent 4,124,607 discloses a process for getting difficult
to dissolve soluble sterol starting materials into a fermentation
medium by dissolving the sterol in an organic solvent with subsequent
removal of the organic solvent by heat or by reduced pressure.

20   U.S. Patent 4,263,253 discloses a process for sterilizing
solids, e.g., pharmaceutical active ingredients, by dissolving the
non-sterile solid in a gas under supercritical conditions, and then
passing the resulting solution through a sterilizing filter to
provide a sterile fluid gas/solid mixture.

25   These above processes are different from the process of this
invention which involves adding a solution of the solute to be
micronized or subdivided in a conventional liquid solvent and then
adding this solution to a compressed liquified or supercritical gas
atmosphere, which gas is essentially an anti-solvent or non-solvent
30   for the solid to be micronized or subdivided as a solid. Moreover,
the processes described above, with the exception of the GAS process
described in Chemical Engineering in July of 1989, which involve the
use of supercritical or liquified gases are limited in their applica-
tion to solids which are soluble in the supercritical gas atmosphere.
35   However, many pharmaceutical, agricultural chemicals, commercial
chemicals, fine chemicals, food items, photographic chemicals, dyes,
explosives, paints, polymers or cosmetics and other solid materials
which need to be further subdivided are not very soluble in the

common and reasonably priced supercritical gas solvents such as carbon dioxide, nitrous oxide, ethylene, fluoroform and the like.

This process invention is intended to provide a solution to the problem of treatment of solids, particularly those which are not 5 soluble enough in a common supercritical or liquified gaseous solvent for making large quantities of solids, which must be finely sub-divided for example, pharmaceuticals, agricultural chemicals, commercial chemicals, fine chemicals, food items, photographic chemicals, dyes, explosives, paints, polymers or cosmetics.

10   SUMMARY OF THE INVENTION

Disclosed is a process for producing a finely divided solid which comprises

(1) dissolving the solid to be finely divided in a liquid carrier solvent to form an injection solution and

15   (2) adding the injection solution of step (1) to a volume of anti-solvent sufficient to precipitate or crystallize the solid.

Also disclosed is a process for producing a sterile finely divided solid which comprises

(1) dissolving the solid to be finely divided in a liquid 20 carrier solvent to form an injection solution,

(2) passing the injection solution through a sterilizing filter,

(3) passing an anti-solvent through a sterilizing filter,

(4) adding the injection solution of step (1) to a volume of anti-solvent sufficient to precipitate or crystallize the solid in a 25 sterilized pressure vessel.

                        BRIEF DESCRIPTION OF THE DRAWING

Figure 1 is a sketch plan and block symbol view of typical apparatus which can be used to operate the process of this invention.

                        DETAILED DESCRIPTION OF THE INVENTION

30   This invention is a process for producing a finely divided solid referred to as "microprecipitation from a compressed gas," or more simply "gas microprecipitation."

The operable solids to be finely divided in the process of the present invention include almost any solid material which needs to be 35 sub-divided in the solid state and which can be dissolved in some liquid carrier solvent. Operable solids include for example, a pharmaceutical, agricultural chemical, commercial chemical, fine chemical, food item, photographic chemical, dye, explosive, paint,

polymer or cosmetic. It is preferred that the solid be a phar-
maceutical (both prescription and non-prescription drugs). It is
preferred that the pharmaceutical be a steroid, benzodiazepene,
penicillin, or cephalosporin. The preferred steroids are those set
forth in CHART A where

(A-I) R_{10} is α-$R_{10\text{-}1}$:β-CH_3, where $R_{10\text{-}1}$ and R_5 are taken
together are -CH_2-CH_2-CO-CH= or -CH=CH-CO-CH=;

(A-II) R_{10} and R_5 taken together are =CH-CH=COH-CH=;

R_6 is α-$R_{6\text{-}1}$:β-H where $R_{6\text{-}1}$ is -H, -F or -CH_3;

R_7 is -H or -S-CO-CH_3;

R_9 is -H, -F, -Cl or -Br;

R_{11} is =O or α-H:β-OH;

R_{16} is α-$R_{16\text{-}1}$:β-$R_{16\text{-}2}$ where $R_{16\text{-}1}$ is -H, -OH or -CH_3 and where
$R_{16\text{-}2}$ is -H or -CH_3 with the proviso that one of
$R_{16\text{-}1}$ or $R_{16\text{-}2}$ is -H;

R_{17} is -H, -CO-$R_{17\text{-}1}$ where $R_{17\text{-}1}$ is C_1-C_5 alkyl;

R_{21} is -Cl, -OH or -O-CO-$R_{21\text{-}1}$ where $R_{21\text{-}1}$ is C_1-C_3 alkyl, with
the proviso that when $R_{16\text{-}1}$ is -OH and when R_{17} is -H, the two groups
can form an acetonide.

Examples of pharmaceuticals include triamcinolone acetonide,
triamcinolone, dexamethasone, dexamethasone sodium phosphate,
methylprednisolone acetate, hydrocortisone, hydrocortisone acetate,
medroxyprogesterone acetate, isoflupredone acetate, alprazolam,
triazolam, penicillin, glyburide, ampicillin, ibuprofen, spec-
tinomycin, erythromycin, flurbiprofen and their salts.

Examples of commercial chemicals include nylon, polystyrene,
benzoic acid, benzene hexachloride and paraffin wax. Examples of
fine chemicals includes citric acid, dichlorobenzedine and benzo-
phenone. Examples of food items include cocoa and powdered milk.
Examples of explosives include plastic explosives, trinitrotoluene
(TNT) and other military munitions. Examples of agricultural
chemicals include herbicides and insecticides.

The solid to be finely divided is first dissolved in a suitable
liquid carrier solvent. The liquid carrier solvent is selected based
on its ability to dissolve the solid to be finely divided, its mis-
cibility with an anti-solvent, toxicity, cost and other factors. The
resulting solution of solid dissolved in the liquid carrier solvent
is called the injection solution.

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The liquid carrier solvent is a conventional liquid solvent (at ambient conditions) in which the solid to be finely divided is quite soluble. In addition the liquid solvent must possess at least partial miscibility with the anti-solvent. Most organic solvents are

5   at least partially miscible with most anti-solvents. Water is only slightly soluble in the anti-solvent carbon dioxide, and even less soluble in ethane, and so, while water may be used as a liquid carrier solvent, the ratio of anti-solvent to injection solution must be kept very high to prevent the formation of a water rich phase in

10 which excessive finely divided solid solute product remains dissolved.

In general, the liquid carrier solvent is chosen for high solubility of the solid to be finely divided, miscibility with the anti-solvent being used, low toxicity, fairly high volatility, non-

15 corrosiveness to the apparatus, and fairly low viscosity for ease of injection. It is understood that for each particular solid there are different preferred liquid carrier solvents which can be readily determined as is known to those skilled in the art. A preferred liquid carrier solvent for any particular solid to be finely divided

20 meets the above criteria and also gives acceptable particle size, crystal form, and low residual solvent levels in the finely divided solid product, for the particular solid being microprecipitated. Suitable liquid carrier solvents include any organic solvent capable of dissolving the solute and mixtures thereof.

25 In general there are no preferred liquid carrier solvents because each solid has different solubility characteristics. Rather each solid will have its own preferred liquid carriers. Common liquid carrier solvents include:

alcohols of the formula R_a-OH where R_a is C_1-C_6 alkyl or ϕ-CH_2-;

30 ethers of the formula R_b-O-R_c where R_b and R_c are the same or different and are C_1-C_4 with the proviso that the total number of carbon atoms not be more than 6, and where R_b and R_c can be taken together with the attached oxygen atom to form a heterocyclic ring consisting of 5-8 atoms;

35 ketones of the formula R_d-CO-R_e where R_d and R_e are the same or different and are -H or C_1-C_4 alkyl with the provisos that (1) R_d and R_e can not both be -H and (2) that the total number of carbon atoms not be more than 6;

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amides of the formula R_f-CO-NR_gR_h where R_f is -H, -CH_3 or -C_2H_5 and R_g and R_h are the same or different and are -H, -CH_3 or -C_2H_5 with the proviso that only one of R_g or R_h can be -H when R_f is -CH_3 or -C_2H_5;

5　　　　esters of the formula R_i-CO-O-R_j where R_i is C_1-C_4 alkyl and R_j is -H or C_1-C_4 alkyl;

aromatic compounds such as benzene optionally substituted with 1 or 2 -Cl or with 1 or 2 -CH_3;

methane type compounds of the formula $C(R_k)_4$ where R_k are the

10　　same or different and are -H or -Cl;

ethane optionally substituted with 1-3 -Cl;

ethene optionally substituted with 1-3 -Cl;

hydrocarbons of the formula $(CH_3$-$(CH_2)_{nl}$-CH_3 where n_1 is 2-6 optionally substituted with 1-4 -Cl; freons; CH_3-CN, glyme and

15　　mixtures thereof. Specific liquid carrier solvents include methanol, ethanol, n- and iso-propanol, n-, sec- and tert-butanol, pentanols, hexanols, heptanols, benzyl alcohol, THF, diethyl ether, methyl-tert-butyl ether, formamide, DMF, N,N-dimethylacetamide, acetone, methyl-ethyl ketone, pentane, hexane, heptane, octane, cyclopentane,

20　　benzene, toluene, xylene, pyridine, methylene chloride, chloroform, carbon tetrachloride, chloromethane, ethylene dichloride, butyl chloride, trichloroethylene, 1,1,2-trichlorotrifluoroethanedioxane, chlorobenzene, ethyl acetate, butyl acetate, acetonitrile, glyme, and mixtures thereof.

25　　The anti-solvent to be used is selected based on several factors of which one of the most important is a low solubility of the pure solid to be finely divided in the anti-solvent and a high solubility of the liquid carrier solvent in the anti-solvent. The selected anti-solvent is chosen to minimize cost, maximize product yield,

30　　minimize toxicity and on other experimental aspects such as producing the correct crystal form and being easily removed from the crystal-line solid, and its being the optimum non-solvent for the solid being finely divided. The selected anti-solvent is one which is at least partially, preferably completely, miscible with the carrier liquid

35　　solvent over the range of pressure and temperature encountered during the operation of the process.

Anti-solvent refers to a gas existing at a temperature equal to or above the pure gas critical temperature and at a pressure equal to

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or above the pure gas critical pressure. Therefore, the term anti-solvent includes supercritical fluids, compressed liquified gases and dense vapors. Because the anti-solvent is chosen which exhibits a small equilibrium solubility for the solid to be microprecipitated,
5   the anti-solvent is an non-solvent in the process. Since the solubility of any solid compound in a anti-solvent is a function of both the temperature and pressure of the supercritical fluid ($T \geq T_c$ and $P \geq P_c$), then optimum yields of finely divided solid may be obtained by adjusting either the temperature or the pressure of the
10   anti-solvent. It is known that lower fluid temperatures favor lower solute solubility. Thus, the process may be run with good results if the temperature of the anti-solvent is less than the critical temperature of the anti-solvent but the pressure is greater than the corresponding vapor pressure of the gas at the selected operating
15   temperature. Under these conditions the supercritical fluid is called a compressed liquified gas, also sometimes referred to as a near-critical liquid (about $0.8T_c < T < T_c$ and $P > P^{vap}$). Thermo-dynamically this criteria is the liquid state. Further, the process also works, though generally not as well, if the anti-solvent is in
20   the dense vapor phase ($T < T_c$ and $P < P_c$), but, for example, inject-ing the injection solvent into a low pressure vapor ($T < T_c$) or a low pressure gas ($T > T_c$) does not produce satisfactory finely divided solid because the anti-solvent is not capable of rapidly diffusing into the stream of impringent injection solvent and therefore not
25   capable of rapidly solubilizing the liquid carrier solvent.

Anti-solvents include supercritical fluids, compressed liquified gases and dense vapors.

Operable anti-solvents include carbon dioxide, ethane, ethylene, nitrous oxide, fluoroform (CHF_3), dimethyl ether, propane, butane,
30   isobutanes, propylene, chlorotrifluormethane ($CClF_3$), sulfur hexa-fluoride (SF_6), bromotrifluoromethane ($CBrF_3$), chlorodifluoromethane ($CHClF_2$), hexafluoroethane, carbon tetrafluoride and mixtures thereof.

Preferred anti-solvents include carbon dioxide, ethane, ethylene
35   and $CClF_3$; more preferred is carbon dioxide.

The solid to be finely divided is dissolved in the liquid carrier solvent to form an injection solution which is usually comprised of a slightly less than saturated concentration of the

solid in the liquid carrier solvent at the temperature which injec-
tion solution is to be maintained. This temperature is usually
chosen as ambient temperature (20-25°) for reasons of operating
convenience, but the injection solution can be prepared and main-
5   tained at higher or lower than ambient temperature if so desired.
Reasons to use other than ambient temperature include the higher
solubility loading of the solid in the liquid carrier solvent at
higher or lower temperatures, thus improving the rate of finely
divided solid product formation, or that the injection solvent
10 temperature influences the particle size, crystal form or habit,
residual solvent content, or other physical property of the ultimate-
ly produced finely divided solid. Although the liquid carrier
solvent may be saturated with solid (now solute), it is generally
preferable to inject slightly less than saturated injection solutions
15 as this condition minimizes the plugging of porous filters, check
valves, and other process equipment through which the injection
solution flows prior to being injected into the anti-solvent.

The injection solution is then added to a comparatively large
volume of the anti-solvent which is under the process conditions a
20 supercritical fluid, liquified compressed gas or dense vapor. In the
usual method of operation the injection solution is pumped into a
stirred autoclave containing the compressed anti-solvent. When the
injection solution (liquid carrier solvent containing dissolved
solid) contacts the anti-solvent, the injection solution is rapidly
25 permeated with the anti-solvent by the normal process of binary dif-
fusion. Since the solubility of the solid is much lower in the anti-
solvent than it is in the liquid carrier solvent, the dissolved solid
precipitates from the anti-solvent/liquid carrier solvent mixture
soon after the contacting is made. Because the contacting, mixing,
30 and diffusion occur on a fast time scale, the solid precipitates out
of the mixture as small, fine particles. If the contacting were made
slower (such as might be achieved by slowly adding anti-solvent to a
prescribed volume of liquid carrier solvent/dissolved solute solu-
tion), then larger sized particles of precipitated solid would be
35 expected to form because of the increased time of good solubility
available for kinetically controlled crystal growth. Slow crystal-
lizations generally produce larger crystals than rapid precip-
itations.

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After a desired quantity of injection solvent has been added to the anti-solvent, the precipitated finely divided solid (product), must be separated from the pressured anti-solvent raffinate. This raffinate is a homogeneous mixture of mostly anti-solvent containing typically 2-10 wt % liquid carrier solvent. Thus, it is important that the liquid carrier solvent be miscible with the anti-solvent at all operating temperatures and pressures encountered in the processing while the raffinate is still in contact with the finely divided solid product. If a temperature, pressure, or composition is reached which causes a liquid carrier solvent-rich second phase to form in the raffinate, finely divided solid product may selectively re-dissolve in this phase and not be recoverable in a finely divided solid state. Two phase gas or liquid formation (a third phase is the solid phase) may be tolerated in the mixture if the finely divided solid is still only sparingly soluble in both phases.

Collection of the finely divided solid product is expediently performed by screening the solid in a sieve filtration operation. The anti-solvent/liquid carrier solvent/finely divided solid precipitate mixture is forced to flow through a fine porosity basket filter located at the bottom of the precipitation chamber while still under full operating pressure. The finely divided solid product is retained by the basket filter while the anti-solvent raffinate passes easily through the bed of collected solid and the sieve filter before being bled from the bottom of the precipitation chamber as clarified filtrate. The low viscosity and low surface tension of the anti-solvent is particularly amenable to fast filtration rates through a packed bed of small particles as opposed to the filtration rate of conventional liquid solvents with their inherently higher viscosities and surface tension effects. In this filtration respect super-critical fluid microprecipitation offers the advantage of rapid filtration rate usually not observed in conventional liquid micro-precipitation, particularly when water is used as the conventional anti-solvent as is common practice.

It is preferred to practice the process of the present invention in a continuous processing mode. In this case the anti-solvent and injection solution are forced into the precipitation chamber and filtered raffinate exits the chamber from the down-stream side of the basket filtration device at such a regulated rate that the chamber

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pressure remains essentially constant with time. When sufficient
solid solute dissolved in the liquid carrier solvent has been added
such that the filtration basket is known to be full of product solid,
then the inlet flow of injection solution is temporarily halted while
5   pure anti-solvent continues to flow into and out of the precipitation
chamber at the operating pressure so as to flush the precipitation
chamber of anti-solvent containing miscible carrier solvent. After a
few residence volumes of pure anti-solvent are forced through the
chamber, the anti-solvent inlet is shut off while the down stream
10   venting of anti-solvent continues. This operation reduces the
chamber pressure to ambient pressure so that the chamber may be
opened and the filtration basket containing finely divided product
solid removed. A thoroughly dry, free flowing finely divided solid
product is obtained. The application of vacuum to the precipitation
15   chamber before opening it may facilitate the complete removal
(degassing) of residual anti-solvent, and/or residual liquid carrier
solvent from the finely divided solid product. Flowing low pressure
nitrogen or other inert gas through the depressurized chamber before
opening also facilitates the complete removal of the anti-solvent
20   which may be adsorbed on the product solid.

In a batch microprecipitation operation, where no exit stream
from the down-stream side of the filtration basket is provided, other
factors may influence the logical end of the microprecipitation
process besides the complete filling of the product collection
25   basket. The batch operation is typically limited by the fact that as
the liquid carrier solvent accumulates in the precipitation chamber,
the solubility of the finely divided solid product also increases in
the liquid carrier solvent/anti-solvent mixture, up to a point where
a significant amount of desired product would be soluble in the
30   raffinate and therefore not collected in the filtration basket
assembly. Further, as injection solution is continuously forced into
the precipitation chamber to effect a batch microprecipitation, the
pressure in the chamber continuously increases which may require
termination of the batch operation so that maximum allowable pressure
35   operating limits on the equipment are not exceeded.

Other reasonable methods of depressurizing and collecting the
finely divided product solid can be envisioned in either the batch or
continuous process operations, and as such do not limit the scope of

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this invention as the primary process effect is that contacting a
solid dissolved in a good liquid carrier solvent with an anti-solvent
produces an isolatable finely divided solid product which possesses
useful and advantageous properties. One such alternative collection
5   scheme would be to not collect the solid product in a sieve filter
basket within the mixing and precipitation chamber, but to have the
microprecipitated product/anti-solvent slurry pass through an exit
channel which branches into two separate filtration/collection
devices such that, with proper valving arrangement, one collection
10   basket device can be depressurized and emptied while the other is
collecting the continuously precipitating product solid. In this way
intermittent suspension of the mixing and precipitation operation
would not have to occur in the mixing chamber to effect emptying the
collected product, and a truly continuous anti-solvent micropre-
15   cipitation process could be performed.

Operable conditions are where the solid is dissolved in the
liquid carrier solvent to the extent of about 1 to about 100% of
saturation for that solid in the particular liquid carrier solvent;
preferred is from about 50 to about 95%, more preferred is from about
20   70 to about 95%.

Optionally, if desired, the process can be operated under
sterile conditions to produce a finely divided sterile crystalline or
powdered product by the use of a sterilizing filter (such as a 0.2
micron average pore size filter) apparatus in the lines leading to
25   the autoclave (1). For example, the dissolved solute/carrier solvent
solution can be filtration sterilized by passing that solution from
the solution feed tank (3) through a sterilizing filter (14) and
passing the compressed liquified or supercritical gas from gas
storage tank (7) through a sterilizing filter (15) prior to mixing of
30   the respective component solution and gas streams in a sterilized
pressure vessel (1).

DEFINITIONS AND CONVENTIONS

The definitions and explanations below are for the terms as used
throughout this entire document including both the specification and
35   the claims.

DEFINITIONS

All temperatures are in degrees Centigrade.
THF refers to tetrahydrofuran.

DMF refers to dimethylformamide.

CO_2 refers to carbon dioxide.

Raffinate refers to the solution or mixture formed containing the liquid carrier solvent dissolved in the anti-solvent with little
5   or no dissolved solid (solute).

Pharmaceutical refers to and includes both prescription and non-prescription drugs.

Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a pharmaco-
10 logical/toxicological point of view and to the manufacturing pharma-ceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavail-ability.

When solvent pairs are used, the ratios of solvents used are
15 volume/volume (v/v).

When the solubility of a solid in a solvent is used the ratio of the solid to the solvent is weight/volume (wt/v).

Term	P, T Conditions	Precise Thermodynamic State
Supercritical fluid	$T \geq T_c$ & $P \geq P_c$	fluid
Compressed liquified gas	$T < T_c$ & $P > P^{vap}$	liquid
Dense vapor	$T < T_c$ & $P < P^{vap}$	gas (vapor)

EXAMPLES

25 Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely
30 illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

EXAMPLE 1   Batch Crystallization

35 A solution of triamcinolone acetonide (6.5 g) in THF (140 ml) is prepared.

Independently and referring to FIGURE 1, the 2-liter autoclave (1) is filled with carbon dioxide at 24° and, by means of the

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diaphragm compressor, the liquid in the autoclave is compressed to
100 bar. The stirring element (2) is then turned on (power source
not shown). The 50 ml vessel (3) is filled with the THF/triamcin-
olone acetonide solution. At time 0, the high pressure metering pump

5   is turned on which begins to deliver the THF/steroid solution into
the agitated carbon dioxide at a flow rate of 7 ml/min. After 5-1/2
minutes 39 ml of THF/steroid solution is delivered and the metering
pump is turned off momentarily. The addition vessel is refilled with
more THF/steroid solution and the metering pump is turned back on.

10   After 12-1/2 minutes, the addition vessel is again nearly empty, so
the metering pump was turned off. A total of 4.0 g of triamcinolone
acetonide is delivered to the autoclave. The pressure in the
autoclave (1) is released by slowly venting the contained carbon
dioxide/THF high pressure liquid mixture through the bottom valve (5)

15   of the autoclave (the flashed gas was vented to the atmosphere). A
wash is then applied to the crystals by refilling the autoclave with
liquid carbon dioxide and pressurizing the vessel to 60 bar, stirring
for 10 minutes, then releasing the pressure out of the bottom valve
(5). The agitator (2) is then turned off. Again carbon dioxide is

20   vented thru the bottom valve (5). The top (8) of the autoclave is
then removed and the filter basket (9) taken out. About 1 gram of
fine, white powder adheres to the sides of the filter basket and
covering most of the bottom 10 micron filter plate (10) in a thin
layer.

25   Upon examination of the powder with a calibrated light micro-
scope, it is found that most of the individual particles are of a
size less than 10 microns with a few being as large as 20-30 microns.
EXAMPLE 2   Continuous Microprecipitation
     This is the preferred mode of operation. Significantly more

30   product can be made per lot.
     A less than saturated injection solution is prepared by dissolv-
ing triamcinolone acetonide (8.0 g) in THF (250 ml) at 20-25°. The
autoclave (1) with filtration basket in place is then pressurized
with CO_2 by means of compressor (11) to 110 bar and heated to 49°

35   while stirring at 2200 RPM. The addition vessel (3) is filled with
the triamcinolone acetonide/THF injection solution (250 ml). The
bottom valve (5) on the autoclave is then opened and CO_2 is allowed
to enter and to vent from the bottom while keeping the autoclave

pressure constant at 110-111 bar by means of the back-pressure regulator (12).

With the pure carbon dioxide flowing at a steady state rate of about 30 g/min, the high pressure metering pump (4) is turned on thus

5 forcing the 20-25° THF/triamcinolone acetonide injection solution into the autoclave (1) at a constant rate of 6.8 ml/min. The injection is continued for 34 minutes until about 230 ml of injection solution is added to continuously flowing carbon dioxide (0.90 kg). The injection solution addition is then stopped, but about 0.2 kg of

10 pure carbon dioxide at 49° and 110 bar is allowed to flow through the autoclave chamber and collected solid product to purge the chamber of residual THF.

The carbon dioxide inlet is then shut off but the carbon dioxide venting is continued from the bottom of the autoclave until the

15 pressure is reduced to ambient pressure. The autoclave is opened and the basket filter assembly is removed. The collection chamber contains triamcinolone acetonide as a fine white dry powder (7.05 g) which corresponds to an 88 wt % recovery. The average particle size of the microprecipitated product is about 5-10 microns by calibrated

20 light microscopy.

CHART A

5
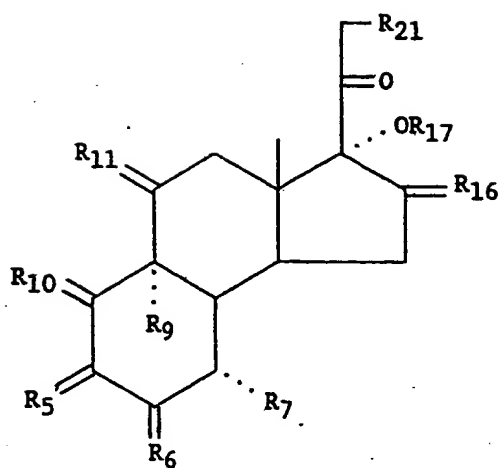
(steroid)

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CLAIMS

1. A process for producing a finely divided solid which comprises

(1) dissolving the solid to be finely divided in a liquid carrier solvent to form an injection solution and

5   (2) adding the injection· solution of step (1) to a volume of anti-solvent sufficient to precipitate or crystallize the solid.

2. A process for producing a finely divided solid according to claim 1 where the solid is a pharmaceutical, agricultural chemical, 10   commercial chemical, fine chemical, food item, photographic chemical, dye, explosive, paint, polymer or cosmetic.

3. A process for producing a finely divided solid according to claim 1 where the solid is a pharmaceutical.

15

4. A process for producing a finely divided solid according to claim 3 where the pharmaceutical is a steroid, benzodiazepene, penicillin, or cephalosporin.

20   5. A process for producing a finely divided solid according to claim 3 where the pharmaceutical is a steroid of the formula
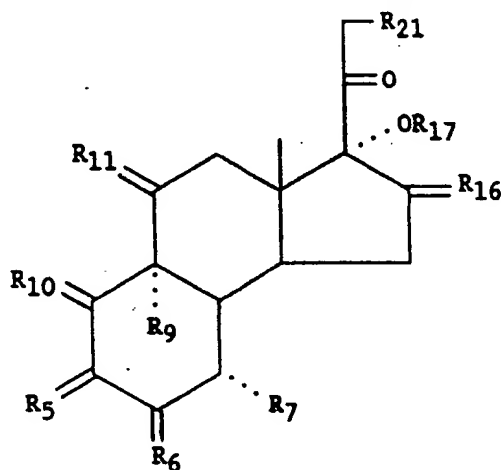
25

(steroid)

30

where

(A-I) R_{10} is α-$R_{10\text{-}1}$:β-CH_3, where $R_{10\text{-}1}$ and R_5 are taken 35   together are $-CH_2$-CH_2-CO-$CH=$ or $-CH=CH$-CO-$CH=$;

(A-II) R_{10} and R_5 taken together are $-CH$-$CH=COH$-$CH=$;

R_6 is α-$R_{6\text{-}1}$:β-H where $R_{6\text{-}1}$ is -H, -F or -CH_3;

R_7 is -H or -S-CO-CH_3;

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R_9 is -H, -F, -Cl or -Br;

R_{11} is =O or α-H:β-OH;

R_{16} is α-R_{16-1}:β-R_{16-2} where R_{16-1} is -H, -OH or -CH$_3$ and where R_{16-2} is -H or -CH$_3$ with the proviso that one of R_{16-1} or R_{16-2} is -H;

R_{17} is -H, -CO-R_{17-1} where R_{17-1} is C_1-C_5 alkyl;

R_{21} is -Cl, -OH or -O-CO-R_{21-1} where R_{21-1} is C_1-C_3 alkyl, with the proviso that when R_{16-1} is -OH and when R_{17} is -H, the two groups can form an acetonide.

6. A process for producing a finely divided solid according to claim 3 where the pharmaceutical is selected from the group consisting of triamcinolone acetonide, triamcinolone, dexamethasone, dexamethasone sodium phosphate, methylprednisolone acetate, hydrocortisone, hydrocortisone acetate, medroxyprogesterone acetate, isoflupredone acetate, alprazolam, triazolam, penicillin, glyburide, ampicillin, ibuprofen, spectinomycin, erythromycin, flurbiprofen and their salts.

7. A process for producing a finely divided solid according to claim 1 where the liquid carrier solvent is any organic solvent capable of dissolving the solute and mixtures thereof.

8. A process for producing a finely divided solid according to claim 1 where the liquid carrier solvent is selected from the group consisting of

R_a-OH where R_a is C_1-C_6 alkyl or ϕ-CH$_2$-;

R_b-O-R_c where R_b and R_c are the same or different and are C_1-C_4 with the proviso that the total number of carbon atoms not be more than 6, and where R_b and R_c can be taken together with the attached oxygen atom to form a heterocyclic ring consisting of 5-8 atoms;

R_d-CO-R_e where R_d and R_e are the same or different and are -H or C_1-C_4 alkyl with the provisos that (1) R_d and R_e can not both be -H and (2) that the total number of carbon atoms not be more than 6;

R_f-CO-NR$_g$R$_h$ where R_f is -H, -CH$_3$ or -C$_2$H$_5$ and R_g and R_h are the same or different and are -H, -CH$_3$ or -C$_2$H$_5$ with the proviso that only one of R_g or R_h can be -H when R_f is -CH$_3$ or -C$_2$H$_5$;

R_i-CO-O-R_j where R_i is C_1-C_4 alkyl and R_j is -H or C_1-C_4 alkyl;

benzene optionally substituted with 1 or 2 -Cl or with 1 or 2

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-CH$_3$;

C(R$_k$)$_4$ where R$_k$ are the same or different and are -H or -Cl;

ethane optionally substituted with 1-3 -Cl;

ethene optionally substituted with 1-3 -Cl;

(CH$_3$-(CH$_2$)$_{n1}$-CH$_3$ where n$_1$ is 2-6 optionally substituted with 1-4 -Cl;

freons;

CH$_3$-CN,

glyme and mixtures thereof.

9. A process for producing a finely divided solid according to claim 1 where the liquid carrier solvent is selected from the group consisting of water, methanol, ethanol, n- and isopropanol, n-, sec- and tert-butanol, pentanols, hexanols, heptanols, benzyl alcohol, THF, diethyl ether, methyl-tert-butyl ether, formamide, DMF, N,N-dimethylacetamide, acetone, methylethyl ketone, pentane, hexane, heptane, octane, cyclopentane, benzene, toluene, xylene, pyridine, methylene chloride, chloroform, carbon tetrachloride, chloromethane, ethylene dichloride, butyl chloride, trichloroethylene, 1,1,2-trichlorotrifluoroethanedioxane, chlorobenzene, ethyl acetate, butyl acetate, acetonitrile, glyme, and mixtures thereof.

10. A process for producing a finely divided solid according to claim 1 where the anti-solvent is a supercritical fluid.

11. A process for producing a finely divided solid according to claim 1 where the anti-solvent is a compressed liquified gas.

12. A process for producing a finely divided solid according to claim 1 where the anti-solvent is a dense vapor.

13. A process for producing a finely divided solid according to claim 1 where the anti-solvent is selected from the group consisting of carbon dioxide, ethane, ethylene, nitrous oxide, fluoroform (CHF$_3$), dimethyl ether, propane, butane, isobutanes, propylene, chlorotrifluormethane (CClF$_3$), sulfur hexafluoride (SF$_6$), bromo-trifluoromethane (CBrF$_3$), chlorodifluoromethane (CHClF$_2$), hexa-fluoroethane, carbon tetrafluoride and mixtures thereof.

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14. A process for producing a finely divided solid according to
claim 1 where the solid is dissolved in the liquid carrier solvent to
the point of about 1 to about 100 weight percent of saturation for
5   that solid in the particular liquid carrier solvent.

15. A process for producing a finely divided solid according to
claim 1 where the liquid carrier solvent is completely miscible with
the anti-solvent.

10

16. A process for producing a finely divided solid according to
claim 1 where the streams of the solid dissolved in the liquid
carrier solvent and the anti-solvent are sterilized by passing these
component streams through sterilizing filters prior to mixing of the
15   component streams in a sterilized pressure vessel.

17. A process for producing a finely divided solid according to
claim 1 where the injection solution is added continuously to the
anti-solvent and the finely divided solid is collected in a con-
20   tinuous manner.

18. A process for producing a finely divided solid according to
claim 1 where the injection solution is added to the anti-solvent and
the finely divided solid is collected in a batch manner.

25

19. A process for producing a finely divided solid according to
claim 1 where the collection of the finely divided solid is aided by
the application of heat, vacuum, forced low pressure inert gas or a
combination thereof.

30

20. A process for producing a sterile finely divided solid which
comprises
        (1) dissolving the solid to be finely divided in a liquid
carrier solvent to form an injection solution,
35   (2) passing the injection solution through a sterilizing filter,
        (3) passing an anti-solvent through a sterilizing filter,
        (4) adding the injection solution of step (1) to a volume of
anti-solvent sufficient to precipitate or crystallize the solid in a

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sterilized pressure vessel.

21. A process for producing a finely divided solid according to claim 20 where the solid is a pharmaceutical, agricultural chemical, commercial chemical, fine chemical, food item, photographic chemical, dye, explosive, paint, polymer or cosmetic.

22. A process for producing a finely divided solid according to claim 20 where the solid is a pharmaceutical.

23. A process for producing a finely divided solid according to claim 20 where the liquid carrier solvent is any organic or aqueous solvent capable of dissolving the solute and mixtures thereof.

24. A process for producing a finely divided solid according to claim 20 where the liquid carrier solvent is selected from the group consisting of

R_a-OH where R_a is -H, C_1-C_6 alkyl or ϕ-CH_2-;

R_b-O-R_c where R_b and R_c are the same or different and are C_1-C_4 with the proviso that the total number of carbon atoms not be more than 6, and where R_b and R_c can be taken together with the attached oxygen atom to form a heterocyclic ring consisting of 5-8 atoms;

R_d-CO-R_e where R_d and R_e are the same or different and are -H or C_1-C_4 alkyl with the provisos that (1) R_d and R_e can not both be -H and (2) that the total number of carbon atoms not be more than 6;

R_f-CO-NR_gR_h where R_f is -H, -CH_3 or -C_2H_5 and R_g and R_h are the same or different and are -CH_3 or -C_2H_5;

R_i-CO-O-R_j where R_i is C_1-C_4 alkyl and R_j is -H or C_1-C_4 alkyl;

benzene optionally substituted with 1 or 2 -Cl or with 1 or 2 -CH_3;

$C(R_k)_4$ where R_k are the same or different and are -H or -Cl;

ethane optionally substituted with 1-3 -Cl;

ethene optionally substituted with 1-3 -Cl;

$(CH_3$-$(CH_2)_{n1}$-CH_3 where n_1 is 2-6 optionally substituted with 1-4 -Cl;

freons;

CH_3-CN,

glyme and mixtures thereof.

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25.   A process for producing a finely divided solid according to
claim 20 where the anti-solvent is selected from the group consisting
of carbon dioxide, ethane, ethylene, nitrous oxide, fluoroform
(CHF$_3$), dimethyl ether, propane, butane, isobutanes, propylene,
chlorotrifluormethane (CClF$_3$), sulfur hexafluoride (SF$_6$), bromo-
trifluoromethane (CBrF$_3$), chlorodifluoromethane (CHClF$_2$), hexa-
fluoroethane, carbon tetrafluoride and mixtures thereof.

10

FIG. 1